EXHIBIT E

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1: Biochem Biophys Res Commun. 1999 Feb 5; 255(1): 164-8. Related Articles, L

ELSEVIER FULL-TEXT ARTICLE

The key amino acid residue of prostaglandin EP3 receptor for governing G protein association and activation steps.

Satoh S, Chang C, Katoh H, Hasegawa H, Nakamura K, Aoki J, Fujita Ichikawa A, Negishi M.

Department of Molecular Neurobiology, Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku Kyoto, 606-8501, Japan.

To assess the role of the conserved DPWXY motif of the seventh transmembrane domain in prostanoid receptor-mediated G protein activation we have mutated the negatively charged Asp-318 in this motif of the Gi-coupled mouse prostaglandin EP3 receptor to uncharged but polar Asn (EP3 D318N) and to the non-polar Leu (EP3-D318L). The EP3 agonist and antagonist showed similar binding affinities for the wild-type and two mutan receptors. The wild-type and EP3-D318N receptors but not EP3-D318L receptor associated with Gi in guanine nucleotide- and pertussis toxin-sensiti manners. On the other hand, the wild-type receptor but not two mutant receptors had the ability to stimulate GTPase activity and to inhibit the adenylate cyclase. These findings demonstrate that the chemical nature of th amino acid residue at position 318 of the seventh transmembrane domain of EP3 receptor dissociates the step of Gi association from that of subsequent activation in the process of the EP3 receptor-Gi coupling. Copyright 1999 Academic Press.

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